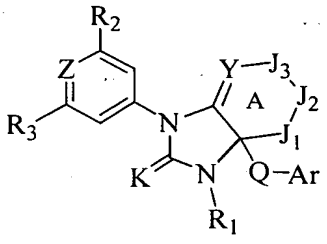
CLAIMS

We claim:

1. A compound of formula (I),



(I),

its enantiomers, diastereomers, or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof, in which:

K is O or S;

Q is a bond, –C(=O)- or branched or straight chain C_{1-4}alkylene optionally substituted with one to two R_4;

Ar is optionally-substituted aryl or heteroaryl;

J_1 is a bond, -N(R_5)-, or –C($R_{6a}R_{7a}$)-;

J_2 is -N(R_5)- or –C($R_{6b}R_{7b}$)-;

J_3 is -N(R_5)- or –C($R_{6c}R_{7c}$)-;

provided, however, that only one of J_1, J_2 and J_3 may be –N(R_5)-, so that ring A is a five-to-six membered cycloalkyl or heterocyclo ring having from 0 to 2 heteroatoms;

Y is N or C(R_8);

Z is N or C(R_9);

R_1 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, -OR_{10}, -$NR_{10}R_{11}$, -C(=O)R_{10}, -CO_2R_{10}, -C(=O)$NR_{10}R_{11}$, -$S(O)_pR_{11a}$, -$SO_2NR_{10}R_{11}$, cycloalkyl, heterocyclo, aryl, and heteroaryl;

R_2 and R_3 are independently selected from hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkenyl, substituted alkenyl, -SR_{12}, -OR_{12}, -$NR_{12}R_{13}$, -CO_2R_{12}, -C(=O)R_{12}, -C(=O)$NR_{12}R_{13}$, aryl, heterocyclo, cycloalkyl, and heteroaryl;

R_4 is selected from OH, O(C_{1-4}alkyl), halogen, cyano, CF_3, OCF_3, NH_2, NH(C_{1-4}alkyl), and N(C_{1-4}alkyl)$_2$;

R_5 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cyano, -OR_{14}, -$NR_{14}R_{15}$, -C(=O)R_{14}, -CO_2R_{14}, -C(=O)$NR_{14}R_{15}$, -$S(O)_pR_{15a}$, -$SO_2NR_{14}R_{15}$, aryl, heterocyclo, cycloalkyl, and heteroaryl; or when R_5 is joined to atom J_1, J_2 or J_3, R_5 may be taken together with one of R_{6a}, R_{6b} or R_{6c} attached to an adjacent atom of ring A to form a fused heterocyclo or heteroaryl ring; or when R_5 is joined to atom J_3, R_5 may be taken together with R_8 to form a fused heterocyclo ring;

R_{6a}, R_{6b}, R_{6c}, R_{7a}, R_{7b}, R_{7c} and R_8 are independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, nitro, cyano, -SR_{16}, -OR_{16}, -$NR_{16}R_{17}$, -C(=O)R_{16}, -CO_2R_{16}, -C(=O)$NR_{16}R_{17}$, -$NR_{16}C(=O)R_{17}$, -$NR_{16}C(=O)OR_{17}$, -$S(O)_qR_{17a}$, -$NR_{16}SO_2R_{17a}$, -$SO_2NR_{16}R_{17}$, aryl, heterocyclo, cycloalkyl, and heteroaryl; or R_{6a} with R_{7a}, or R_{6b} with R_{7b}, or R_{6c} with R_{7c} are taken together to form a keto group (=O) or a spiro cycloalkyl or heterocyclo ring; or R_{6b} taken together with either R_{6a} or R_{6c} may form a fused benzo, cycloalkyl, heterocyclo, or heteroaryl ring; or R_{6c} taken together with R_8 may form a fused cycloalkyl or heterocyclo;

R_9 is selected from hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkenyl, substituted alkenyl, -SR_{18}, -OR_{18}, -$NR_{18}R_{19}$, -CO_2R_{18}, -C(=O)R_{18}, -C(=O)$NR_{18}R_{19}$, aryl, heterocyclo, cycloalkyl, and heteroaryl;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} (i) are selected independently of each other from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclo; or (ii) any two of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} when attached to the same nitrogen atom may be taken together to form a heteroaryl or heterocyclo ring, with the remainder of R_{10}, R_{11}, R_{12}, R_{13},

R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} being selected independently from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclo;

R_{11a}, R_{15a}, and R_{17a} are independently selected from alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclo;

p is 1, 2, or 3; and

q is 1, 2, or 3.

2. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein:

K is O;

Q is a $-CH_2-$;

Ar is phenyl optionally substituted one to three R_{20};

R_1 is selected from hydrogen, C_{1-6}alkyl, -C(=O)H, -C(=O)(C_{1-6}alkyl), -CO_2H, -CO_2(C_{1-6}alkyl), or C_{1-6}alkyl substituted with one to two of hydroxy, –O(C_{1-6}alkyl), -C(=O)H, -C(=O)(C_{1-6}alkyl), -CO_2H, -CO_2(C_{1-6}alkyl), -C(=O)NH_2, -C(=O)NH_2, - C(=O)NH(C_{1-4}alkyl), -C(=O)N(C_{1-4}alkyl)$_2$, -NH_2, -NH(C_{1-4}alkyl), and -N(C_{1-4}alkyl)$_2$;

R_2 and R_3 are selected from halogen, (C_{1-4})alkyl, cyano, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, nitro, phenyloxy, benzyloxy, and phenylthio;

R_{20} at each occurrence is independently selected from halogen, C_{1-4}alkyl, hydroxy, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, cyano, nitro, -CO_2H, -C(=O)H, -CO_2(C_{1-4})alkyl, -C(=O) (C_{1-4})alkyl, -C(=O)NH(CH_2)$_r$$CO_2$H, -C(=O)NH($CH_2$)$_r$$CO_2$($C_{1-4}$alkyl), and S(O)$_2$($C_{1-4}$alkyl); or from phenyl, benzyl, phenyloxy, benzyloxy and heteroaryl in turn optionally substituted with one to two of halogen, C_{1-4}alkyl, hydroxy, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, cyano, nitro, -CO_2H, -C(=O)H, -CO_2(C_{1-4})alkyl, and/or -C(=O) (C_{1-4})alkyl; or alternatively, two R_{20} groups join together with each other to form a fused benzo ring; and

r is 1, 2, 3, or 4.

3. A compound according to claim 2, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein

J_1 is a bond or $-CHR_{6a}-$;

J_2 is $-CHR_{6b}-$;

J_3 is $-CHR_{6c}-$;

Y is $C(R_8)$;

R_{6a}, R_{6b}, R_{6c} and R_8 are independently selected from

a) hydrogen, halogen, and cyano;

b) $-SR_{16}$, $-OR_{16}$, $-NR_{16}R_{17}$, $-C(=O)R_{16}$, $-CO_2R_{16}$, $-C(=O)NR_{16}R_{17}$, $-NR_{16}C(=O)R_{17}$, $-NR_{16}C(=O)OR_{17}$, $-S(O)_qR_{17a}$, $-NR_{16}SO_2R_{17a}$, and $-SO_2NR_{16}R_{17}$; and

c) C_{1-4}alkyl, phenyl, four to seven membered heterocyclo, C_{3-7}cycloalkyl, and five to six membered heteroaryl, each of which in turn is optionally substituted with one to two groups selected from R_{22};

R_{16} and R_{17} are selected independently of each other from hydrogen, C_{1-6}alkyl, phenyl, four to seven membered heterocyclo, C_{3-7}cycloalkyl, and five to six membered heteroaryl, each of which in turn is optionally substituted with one to two groups selected from R_{23};

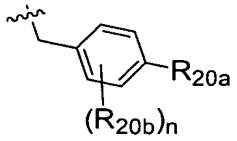
R_{17a} is C_{1-6}alkyl, phenyl, four to seven membered heterocyclo, C_{3-7}cycloalkyl, five to six membered heteroaryl each of which is optionally substituted with one to two groups selected from R_{23}; and

R_{22} and R_{23} are at each occurrence selected independently from halogen, cyano, C_{1-4}alkyl, hydroxy, trifluoromethyl, trifluoromethoxy, $-O(C_{1-4}$alkyl), $-C(=O)H$, $-C(=O)(C_{1-6}$alkyl), $-CO_2H$, $-CO_2(C_{1-6}$alkyl), $-C(=O)NH_2$, $-C(=O)NH_2$, $-C(=O)NH(C_{1-4}$alkyl), $-C(=O)N(C_{1-4}$alkyl$)_2$, $-NH_2$, $-NH(C_{1-4}$alkyl), $-N(C_{1-4}$alkyl$)_2$, hydroxy(C_{1-4})alkyl, methoxy(C_{1-4})alkyl, ethoxy(C_{1-4})alkyl, amino(C_{1-4})alkyl, and halo(C_{1-4})alkyl.

4. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein:

R_1 is hydrogen, C_{1-6}alkyl, -C(=O)(C_{1-6}alkyl), or C_{1-6}alkyl substituted with one of -C(=O)H, -C(=O)(C_{1-6}alkyl), -CO_2H, or -CO_2(C_{1-6}alkyl).

5. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein Q-Ar together form:



wherein

R_{20a} and R_{20b} are independently selected from halogen, C_{1-4}alkyl, hydroxy, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, cyano, nitro, -CO_2H, -C(=O)H, -CO_2(C_{1-4})alkyl, -C(=O) (C_{1-4})alkyl, -C(=O)NH(CH_2)$_r$$CO_2$H, -C(=O)NH($CH_2$)$_r$$CO_2$($C_{1-4}$alkyl), and S(O)$_2$($C_{1-4}$alkyl); or from phenyl, benzyl, phenyloxy, benzyloxy and heteroaryl in turn optionally substituted with one to two of halogen, C_{1-4}alkyl, hydroxy, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, cyano, nitro, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CO_2H, -C(=O)H, -CO_2(C_{1-4})alkyl, and/or -C(=O) (C_{1-4})alkyl; or alternatively, two R_{20b} groups join together with each other or one R_{20b} joins together with R_{20a} to form a fused benzo ring;

n is 0, 1, or 2; and

r is 1, 2, 3, or 4.

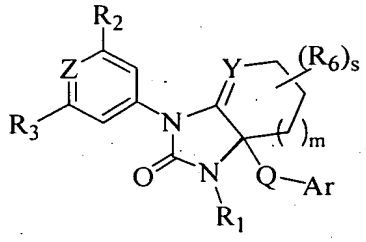
6. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein J_1, J_2 and J_3 are each –CH_2-.

7. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein Y is CH.

8. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein R_2 and R_3 are both halogen.

9. A compound according to claim 1, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, wherein Z is CH.

10. A compound having the formula (Ia),



(Ia),

its enantiomers, diastereomers, or a pharmaceutically-acceptable salt, hydrate, solvate, or prodrug thereof, in which:

Q is $-C(=O)-$ or $-(CHR_{4a})_t-$

Ar is aryl or heteroaryl optionally substituted with one to three R_{20};

Y is N or $C(R_8)$;

Z is N or $C(R_9)$;

R_1 is selected from hydrogen, C_{1-6}alkyl, -C(=O)H, $-C(=O)(C_{1-6}alkyl)$, $-CO_2H$, $-CO_2(C_{1-6}alkyl)$, or C_{1-6}alkyl substituted with one to two of hydroxy, $-O(C_{1-6}alkyl)$, -C(=O)H, $-C(=O)(C_{1-6}alkyl)$, $-CO_2H$, $-CO_2(C_{1-6}alkyl)$, $-C(=O)NH_2$, $-C(=O)NH_2$, $-C(=O)NH(C_{1-4}alkyl)$, $-C(=O)N(C_{1-4}alkyl)_2$, $-NH_2$, $-NH(C_{1-4}alkyl)$, and $-N(C_{1-4}alkyl)_2$;

R_2 and R_3 are independently selected from halogen, (C_{1-4})alkyl, cyano, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, nitro, phenyloxy, benzyloxy, and phenylthio;

R_{4a} is selected from hydrogen, OH, $O(CH_3)$, $O(CH_2CH_3)$, halogen, cyano, CF_3, OCF_3, NH_2, $NH(CH_3)$, and $N(CH_3)_2$;

R_6 and R_8 at each occurrence are independently selected from (a) halogen, nitro, and cyano; or from (b) $-SR_{16}$, $-OR_{16}$, $-NR_{16}R_{17}$, $-C(=O)R_{16}$, $-CO_2R_{16}$, $-C(=O)NR_{16}R_{17}$, $-NR_{16}C(=O)R_{17}$, $-NR_{16}C(=O)OR_{17}$, $-S(O)_qR_{17a}$, $-NR_{16}SO_2R_{17a}$, and $-SO_2NR_{16}R_{17}$; or from (c) alkyl, alkenyl, aryl, heterocyclo, cycloalkyl, and heteroaryl, in turn optionally substituted with one to two groups selected from R_{22}; and/or (d) two R_6 groups taken together form keto (=O), with the remainder of the R_6 groups selected from (a), (b), and (c);

R_9 is selected from hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkenyl, substituted alkenyl, $-SR_{18}$, $-OR_{18}$, $-NR_{18}R_{19}$, $-CO_2R_{18}$, $-C(=O)R_{18}$, $-C(=O)NR_{18}R_{19}$, aryl, heterocyclo, cycloalkyl, and heteroaryl;

R_{16} and R_{17} are selected independently of each other from hydrogen, C_{1-6}alkyl, phenyl, four to seven membered heterocyclo, C_{3-7}cycloalkyl, and five to six membered heteroaryl, each of which in turn is optionally substituted with one to two groups selected from R_{23};

R_{17a} is C_{1-6}alkyl, phenyl, four to seven membered heterocyclo, C_{3-7}cycloalkyl, five to six membered heteroaryl each of which is optionally substituted with one to two groups selected from R_{23};

R_{20} at each occurrence is selected from halogen, C_{1-6}alkyl, hydroxy, (C_{1-4})alkoxy, (C_{1-4})alkylthio, cyano, nitro, $-CO_2H$, $-C(=O)H$, $-CO_2(C_{1-4})$alkyl, $-C(=O)(C_{1-4})$alkyl, $-C(=O)NH(CH_2)_rCO_2H$, $-C(=O)NH(CH_2)_rCO_2(C_{1-4}$alkyl), $S(O)_2(C_{1-4}$alkyl), phenyl, benzyl, phenyloxy, benzyloxy, five to six membered heteroaryl, C_{3-7}cycloalkyl, and four to seven membered heterocyclo, wherein each of the alkyl, alkoxy, and cyclic groups in turn are optionally substituted with one to three of R_{24};

R_{22}, R_{23} and R_{24} are at each occurrence selected independently from halogen, cyano, nitro, C_{1-6}alkyl, hydroxy, trifluoromethyl, trifluoromethoxy, $-O(C_{1-6}$alkyl), $-C(=O)H$, $-C(=O)(C_{1-6}$alkyl), $-CO_2H$, $-CO_2(C_{1-6}$alkyl), $-C(=O)NH_2$, $-C(=O)NH_2$, $-C(=O)NH(C_{1-4}$alkyl), $-C(=O)N(C_{1-4}$alkyl$)_2$, $-NH_2$, $-NH(C_{1-}$

$_4$alkyl), -N(C_{1-4}alkyl)$_2$, hydroxy(C_{1-4})alkyl, methoxy(C_{1-4})alkyl, ethoxy(C_{1-4})alkyl, amino(C_{1-4})alkyl, and halo(C_{1-4})alkyl;

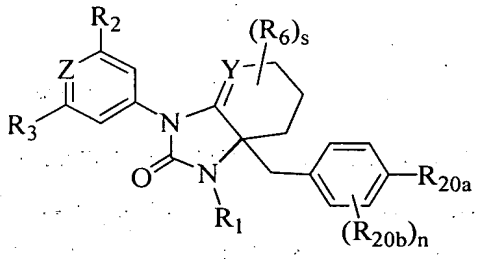
m is 0 or 1;

p and *q* are independently 1, 2, or 3;

r and *s* are 0, 1, 2, 3 or 4; and

t is 0, 1 or 2.

11. A compound according to claim 10 having the formula,



or a pharmaceutically-acceptable salt, hydrate, solvate, or prodrug thereof, in which:

R_{20a} and R_{20b} are independently selected from halogen, C_{1-4}alkyl, hydroxy, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, cyano, nitro, -CO_2H, -C(=O)H, -CO_2(C_{1-4})alkyl, -C(=O) (C_{1-4})alkyl, -C(=O)NH(CH_2)$_r$$CO_2$H, -C(=O)NH($CH_2$)$_r$$CO_2$($C_{1-4}$alkyl), and S(O)$_2$($C_{1-4}$alkyl); or from phenyl, benzyl, phenyloxy, benzyloxy and heteroaryl in turn optionally substituted with one to two of halogen, C_{1-4}alkyl, hydroxy, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, cyano, nitro, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CO_2H, -C(=O)H, -CO_2(C_{1-4})alkyl, and/or -C(=O) (C_{1-4})alkyl; or alternatively, two R_{20b} groups join together with each other or one R_{20b} joins together with R_{20a} to form a fused benzo ring; and

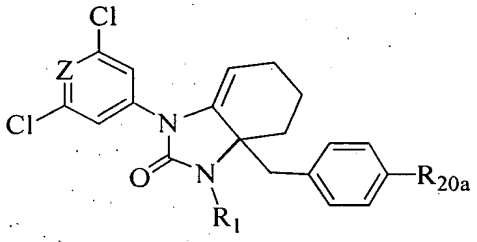
n is 0, 1 or 2.

12. A compound according to claim 11, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, in which R_1 is C_{1-4} alkyl.

13. A compound according to claim 11, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, in which R_2 and R_3 are both halogen.

14. A compound according to claim 11, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, in which R_{20a} is cyano or halogen.

15. A compound according to claim 11, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, having the formula,



16. A compound according to claim 15, or a pharmaceutically-acceptable salt, hydrate, prodrug, or enantiomer thereof, in which Z is CH, R_1 is methyl or ethyl, and R_{20a} is cyano or halogen.

17. A pharmaceutical composition comprising at least one compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.

18. A pharmaceutical composition comprising at least one compound according to claim 10 and a pharmaceutically acceptable carrier or diluent.

19. A method of inhibiting an LFA-1/ICAM-associated condition in a mammal comprising administering to the mammal a therapeutically-effective amount of a compound according to claim 1.

20. The method of claim 19 in which LFA-1/ICAM-associated condition is selected from acute or chronic graft vs host reactions, acute or chronic transplant rejection, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, osteoporosis, diabetes, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis, multiple organ injury syndrome, myocardial infarction, atherosclerosis, stroke, reperfusion injury, acute glomerulonephritis, vasculitis, thermal injury, necrotizing enterocolitis, granulocyte transfusion associated syndrome, Sjogren's syndrome, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, psoriasis, asthma, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), hepatitis B, hepatitis C, organ-tissue autoimmune disease, autoimmune thyroiditis, uveitis, systemic lupus erythematosis, Addison's disease, autoimmune polyglandular disease, and Grave's disease.